BIOSERVICE

SCIENTIFIC LABORATORIES GmbH

Acute Eye Irritation/Corrosion

with

Niobium

Report

Version: Final

Date: 28 October 2009

BSL BIOSERVICE Study No.: 092571A

Sponsor:

CBMM Europe BV

WTC H- Tower

Zuidplein 96

1077 XV, Amsterdam

The Netherlands

BSL BIOSERVICE Scientific Laboratories GmbH
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Amtsgericht München, HRB 109 770
Erfüllung und Gerichtsstand München
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Deutsche Bank München, BLZ 700 700 24, Kto. 9 407 750, Swift-BIC: DEUTDEDBMUC, IBAN: DE52 7007 0024 0940 7750 00

GLP zertifiziert

Akkreditiert durch
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
ZLG-P-986.96.01

1. Copy of the GLP Certificate

BAYERISCHES LANDESAMT
FÜR GESUNDHEIT UND LEBENSMITTELSICHERHEIT,
LANDESINSTITUT FÜR ARBEITSSCHUTZ UND PRODUKTSICHERHEIT
Pfarrstraße 3 · 80538 München · Telefon (089) 21 84-0

GLP-Bescheinigung/Statement of GLP Compliance
(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at:

☒ Prüfeinrichtung/Test facility ☐ Prüfstandort/Test site

BSL Bioservice Scientific Laboratories GmbH
Behringstrasse 6 - 8
82152 Planegg

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/Areas of Expertise
(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

2 Prüfungen auf toxikologische Eigenschaften
3 Prüfungen auf mutagene Eigenschaften
9 Sonstige Prüfungen:
a) Mikrobiologische Sicherheitsprüfungen
b) Wirksamkeitsprüfungen an Zellkulturen

Datum der Inspektion/Date of Inspection
(Tag.Monat.Jahr/day.month.year)
16./17.09.2008

Die/Der genannte Prüfeinrichtung/Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/ diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Based on the inspection report it can be confirmed, that this test facility/test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

München, 06.04.2009

Ritter
Leitender Gewerbedirektor

2. Contents

3. List of Tables and Figures

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4. Preface

4.1. Abbreviations

BGBl.	Bundesgesetzblatt
GLP	Good Laboratory Practice
OECD	Organisation of Economic Cooperation and Development
QA	Quality Assurance
QAU	Quality Assurance Unit
SOP	Standard Operating Procedures

4.2. General

Sponsor:	CBMM Europe BV WTC H- Tower Zuidplein 96 1077 XV, Amsterdam The Netherlands
Study Monitor:	Mr Jorge Davo CBMM Companhia Brasileira de Metalurgia e Mineração Córrego da Mata s/n 38183-903 Araxá - MG Brasil
Test Facility:	BSL BIOSERVICE Scientific Laboratories GmbH Behringstraße 6/8 82152 Planegg Germany
BSL BIOSERVICE Study No.:	092571A
Test Item:	Niobium
Title:	Acute Eye Irritation/Corrosion with Niobium

4.3. Project Staff

Study Director:	Dr. Daniela Stelter
Deputy Study Director:	Dr. Achim Albrecht
Management:	Dr. Wolfram Riedel Dr. Angela Lutterbach
Head of Quality Assurance Unit:	Dipl.-Biol. Uwe Hamann

4.4. Schedule

Arrival of the Test Item:	20 July 2009
Date of Draft Study Plan:	31 July 2009
Date of Final Study Plan:	31 August 2009
Start of Experiment:	14 September 2009
End of Experiment:	18 September 2009
Date of Draft Report:	19 October 2009
Date of Final Report:	28 October 2009

5. Project Staff Signatures

Study Director — Dr. Daniela Stelter

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Date: 28 Oct 2009

Management

.....

Print Name: Dr. Wolfram Riedel

Date: 28 Oct 2009

6. Quality Assurance

6.1. GLP Compliance

This study was conducted to comply with:

Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on June 20, 2002 (BGBl. 1 Nr. 40 S. 2090), revised October 31, 2006 (BGBl. I Nr. 50 S. 2407).

OECD Principles of Good Laboratory Practice (as revised in 1997); OECD Environmental Health and Safety Publications; Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organisation for Economic Co-operation and Development, Paris 1998.

This study was assessed for compliance with the study plan and the Standard Operating Procedures of BSL BIOSERVICE. The study and/or the test facility were periodically inspected by the Quality Assurance unit according to the corresponding SOPs. These inspections and audits were carried out by the Quality Assurance unit, personnel independent of staff involved in the study. A signed Quality Assurance Statement, listing all performed audits, is included in the report.

6.2. Guidelines

This study followed the procedures indicated by internal BSL BIOSERVICE SOPs and the following internationally accepted guidelines and recommendations:

First Addendum to OECD Guidelines for Testing of Chemicals, Section 4, No. 405, "Acute Eye Irritation/Corrosion" adopted 24 April 2002

Commission Regulation (EC) No 440/2008, L 142, Annex Part B, 30 May 2008

EPA Health Effects Test Guidelines, OPPTS 870.2400 "Acute eye irritation", EPA 712-C-98-195 (August 1998)

ISO 10993-12: 2007 "Sample preparation and reference materials"

6.3. Archiving

The following records will be stored in the scientific archives of BSL BIOSERVICE Scientific Laboratories GmbH according to the GLP Regulations:

A copy of the final report, the study plan and a documentation of all raw data generated during the conduct of the study (documentation forms as well as any other notes of raw data, printouts of instruments and computers) and the correspondence with the Sponsor concerning the study.

If test item is left, a sample will be stored according to the period fixed by the GLP Regulations. Samples that are unstable may be disposed of before that time. No raw data or material relating to the study will be discarded without the Sponsor's prior consent. Unless otherwise agreed upon, the remaining test item will be discarded three months after the release of the report.

7. Statement of Compliance

BSL BIOSERVICE-Study No.:	092571A
Test Item:	Niobium
Title:	Acute Eye Irritation/Corrosion with Niobium
Study Director:	Dr. Daniela Stelter

This study performed in the test facility BSL BIOSERVICE Scientific Laboratories GmbH was conducted in compliance with Good Laboratory Practice Regulations:

Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on June 20, 2002 (BGBl. Nr. 40 S. 2090), revised October 31, 2006 (BGBl. I Nr. 50 S. 2407).

"OECD Principles of Good Laboratory Practice (as revised in 1997)", Paris 1998.

There were no circumstances that may have affected the quality or integrity of the study.

Study Director: Dr. Daniela Stelter

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Date: 06 Nov 2009

8. Statement of the Quality Assurance Unit

BSL BIOSERVICE-Study No.:	092571A
Test Item:	Niobium
Title:	Acute Eye Irritation/Corrosion with Niobium
Study Director:	Dr. Daniela Stelter

This report was audited by the Quality Assurance unit and the conduct of this study was inspected on the following dates:

Phases of QAU Inspections	*Dates of QAU Inspections*	*Dates of Reports to the Study Director and Management*
Audit Final Study Plan:	03 September 2009	03 September 2009
Audit Experimental Phase (Method Audit):	03 June 2009	03 June 2009
Audit Final Report:	03 November 2009	03 November 2009

This report reflects the raw data.

Member of the
Quality Assurance unit: Anne Krabiell

Print Name:

Dipl.oec.troph (FH)
Anne Krabiell

Date: 06 Nov 2009

9. Summary

On the basis of the test results given below and in conformity with the criteria given in Annex VI to Commission Directive 2001/59/EC as well as in Annex I of Regulation (EC) 1272/2008, the substance should be:

classified as irritant	[ ]
not classified	[X]

Species/strain:	New Zealand White Rabbits Crl: KBL (NZW)
Number of animals:	3
Extraction vehicle:	physiological saline 0.9% NaCl
Amount of substance:	0.1 mL test item extract per test site
First time of effects:	24 hours post-instillation (1 out of 3 animals)
Last time of effects:	24 hours post-instillation (1 out of 3 animals)
Reversibility of the observed effects:	

Animals no. 1 and 2: No effects were observed.

Animal no. 3: the changes were fully reversible within 48 hours post instillation.

Method:	OECD 405 EC 440/2008 OPPTS 870.2400

The calculated mean scores did not exceed the limit values according to Directive 2001/59/EC and Regulation (EC) 1272/2008 (see *Evaluation of Results, p. 18*) in any case (table 1).

Table 1: Mean Values of Eye Irritation Scores – (24, 48, 72 Hour Reading)

Animal number	*Sex*	*Cornea opacity*	*Iris*	*Conjunctival redness*	*Conjunctival chemosis*
1	female	0.00	0.00	0.00	0.00
2	female	0.00	0.00	0.00	0.00
3	female	0.00	0.00	0.33	0.00

9.1. Conclusions

Under the conditions of the present study, single ocular instillation of the extract of the test item Niobium to rabbits at a dose of 0.1 mL produced slight irritant effects in 1 out of 3 animals, which were fully reversible within 48 hours. Neither mortalities nor significant clinical signs of toxicity were observed.

In conformity with the EC criteria for classification and labelling requirements for dangerous substances and preparations according to Annex VI of Commission Directive 2001/59/EC and Annex I of Regulation (EC) 1272/2008, the test item Niobium does not have to be classified and has no obligatory labelling requirement for eye irritation (for details see *Evaluation of Results*).

10. Aim of the Study

10.1. Justification for Selection of the Test System

The test for acute eye irritation/corrosion is performed on the rabbit.

In the assessment and evaluation of the toxic characteristics of a test item, determination of the irritant and/or corrosive effects on eyes is an important initial step.

Test items meeting any of the following criteria will not be tested:

a) materials that have predictable corrosive potential based on structure-activity relationships and/or physicochemical properties such as strong acidity or alkalinity, e.g., when the material to be applied has a pH of ≤ 2 or ≥ 11.5.

b) materials which have shown definite corrosive or severe skin irritancy in a dermal study.

c) materials that have been shown to be corrosive by the *in-vitro* skin corrosion test.

10.2. Justification for Selection of the Test Method

No validated *in vitro* method is available for assessing acute eye irritation/corrosion.

11. Materials and Methods

11.1. Characterisation of the Test Item

The test item and the information concerning the test item were provided by the Sponsor. All data related to the test item are the responsibility of the Sponsor and have not been verified by the test facility.

Name:	Niobium
Product:	Niobium Metal (Nb)
CAS no.:	7440-03-1
Batch no.:	AD/4202
Chemical name:	niobium
Density:	~8.5 g / cm^3
Active components:	Nb - >98.5%
Colour:	silver grey metalic
Physical state:	solid
Storage:	at room temperature
Stability:	stable
Safety precautions:	Routine hygienic procedures were sufficient to assure personnel health and safety.

11.2. Preparation of the Test Item

Due to its physical properties the test item had to be extracted before the application.

The extraction of the test item was performed according to ISO 10993-12.

In total a ratio of 4 g of sample to 20 mL of extraction medium was used.

Extraction conditions: 37 ± 1 °C for 72 ± 2 h, under agitation

Extraction medium:

- physiological saline 0.9% NaCl, B. Braun Melsungen, lot no. 9181A121, expiry date: March 2012

Up to the next-day administration the extract was stored at room temperature.

11.3. Weight-of-the-evidence Analysis

In order to avoid the unnecessary use of animals and to minimise any testing that is likely to produce severe responses in animals, a weight-of-the-evidence analysis was performed with the available data (data from the test substance data sheet). The paperwork is archived in the project file. Additionally the confirmation in writing that the studies are required for submission to regulatory authorities or to fulfil obligations postulated by law was taken into account.

11.4. Test System

Species/strain: Healthy New Zealand White Rabbits, Crl: KBL (NZW)

Source: Charles River Deutschland, 97633 Sulzfeld, Germany

Sex: female

Body weight at the beginning of the study: > 2 kg

Age at the beginning of the study: approximately 23 weeks old

Number of animals: 3

The animals were derived from a controlled full-barrier maintained breeding system (SPF). According to Art. 9.2, No.7 of the German Act on Animal Welfare the animals were bred for experimental purposes.

11.4.1. Housing and Feeding Conditions

- Semi barrier in an air-conditioned room
- Temperature: 18 ± 3°C (recommendations of TVT, GV-SOLAS; see References)
- Relative humidity: 55 ± 10%
- Artificial light, sequence being 12 hours light, 12 hours dark
- Air change: at least 10 x / hour
- Free access to autoclaved hay and to Altromin 2123 maintenance diet for rabbits (lot no. 1306), rich in crude fibre
- Free access to tap water (drinking water, municipal residue control, microbiol. controlled periodically)
- Certificates of food, water and bedding are filed at BSL BIOSERVICE
- Housed in ABS - plastic rabbit cages, floor 4200 cm^2
- Adequate acclimatisation period (at least 5 days)

11.5. Preparation of the Animals

Approximately 24 hours before the test and immediately prior to the application both eyes of each animal were examined. A health inspection was performed to ensure the good state of health of the animals. None of the animals showed eye irritation, ocular defects, or pre-existing corneal injury.

11.6. Initial Test (In Vivo Eye Irritation/Corrosion Test Using One Animal)

The in vivo test was performed initially using one animal.

11.7. Application

The test item extract was applied at a single dose in the conjunctival sac of one eye of each test animal after pulling the lower lid away from the eyeball. The lids were then gently held together for about 1 second in order to prevent loss of the material.

The untreated contralateral eye of each animal served as control.

The eyes were not rinsed.

11.8. Dose Level

A dose of 0.1 mL of the test item extract was applied to the test site.

11.9. Confirmatory Test

The results of the initial test did not indicate the test item to be corrosive or a severe irritant to the eye using the procedure described. In order to confirm the response, two additional animals were treated in the same manner.

11.10. Observation Period

The animals were observed for 72 hours after dosing.

11.11. Clinical Observation

The eyes were examined for signs of irritation throughout the observation period. The eye irritation was scored and recorded according to the grades in the table below.

For the calculation only the 24, 48 and 72 hour readings were used.

At the end of the observation period the treated eyes were examined with the aid of a fluorescein solution (Fluoreszein SE Thilo®, lot no. H 801, expiry date: January 2010).

Table 2: Grading of Ocular Lesion

Cornea: Degree of Density (Opacity, area most dense taken for reading)	*Score*
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible	1
Easily discernible translucent area, details of iris slightly obscured	2
Nacreous area, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through the opacity	4

Iris	*Score*
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia, or injection; iris reactive to light (a sluggish reaction is considered to be an effect)	1
Hemorrhage, gross destruction, or no reaction to light	2

Conjunctiva *Redness (refers to palpebral and bulbar conjunctiva: excluding cornea and iris)*	*Score*
Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3

Conjunctiva *Chemosis* *Swelling (refers to lids and/or nictitating membranes)*	*Score*
Normal	0
Some swelling above normal	1
Obvious swelling, with partial eversion of lids	2
Swelling, with lids about half closed	3
Swelling with lids more than half closed	4

11.12. Evaluation of Results

Individual reactions of each animal were recorded at each time of observation.

Nature, severity and duration of all lesions observed were described.

For the calculation only the 24-, 48- and 72-hour readings were used.

On the basis of the test results, the test substance was classified in any of the following classes in conformity with the criteria given in Annex VI to Commission Directive 2001/59/EC:

R36 Irritating to eyes

- Substances and preparations which, when applied to the eye of the animal, cause significant ocular lesions which occur within 72 hours after exposure and which persists for at least 24 hours.

Ocular lesions are significant if the mean scores of the eye irritation test cited in Annex B.5 to Commission Regulation (EC) No. 440/2008, L 142 have any of the following values:

- cornea opacity equal to or greater than 2 but less than 3,
- iris lesion equal to or greater than 1 but not greater than 1.5,
- redness of the conjunctiva equal to or greater than 2.5,
- oedema of the conjunctiva (chemosis) equal to or greater than 2,

or, in case where Annex B.5 test have been completed using three animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than 1 but less than 2 and for redness of the conjunctiva the value should be equal to or greater than 2.5.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

- Substances or preparations which cause significant ocular lesions, based on practical experience in humans.
- Organic peroxides except where evidence to the contrary is available.

R41 Risk of serious damage to eyes

Substances and preparations which, when applied to the eye of the animal cause severe ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are severe if the means of the scores of the eye irritation test cited in Annex B.5 to Commission Regulation (EC) No. 440/2008, L 142 have any of the values:

- cornea opacity equal to or greater than 3,
- iris lesion greater than 1.5.

The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the values:

- cornea opacity equal to or greater than 3,
- iris lesion equal to 2.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

Ocular lesions are also severe when they are still present at the end of the time of observation.

Ocular lesions are also severe if the substance or preparation causes irreversible colouration of the eyes.

- Substances and preparations which cause severe ocular lesions, based on practical experience in humans.

Note:

When a substance or preparation is classified as corrosive and assigned R34 or R35, the risk of severe damage to eyes is considered implicit and R41 is not included in the label.

On the basis of the test results, the following risk phrases shall be assigned in conformity with the criteria given in Annex I of Regulation (EC) 1272/2008:

Eye irritant Category 1:

Irreversible effects on the eyes/Serious damage to the eyes

An eye irritant category 1 is a test material that produces:

- At least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or that have not fully reversed within 21 days; and/or
- At least in 2 of 3 animals, a positive response of
  - (i) Corneal opacity ≥ 3; and/or
  - (ii) Iritis > 1.5

  Calculated as the mean scores following the grading at 24, 48 and 72 hours after instillation of the test material.

Eye irritant Category 2:

Reversible effects on the eyes/Irritating to the eyes

An eye irritant category 2 is a test material that produces:

- At least in 2 of 3 animals, a positive response of
  - (i) Corneal opacity ≥ 1; and/or
  - (ii) Iritis ≥ 1; and/or
  - (iii) Conjunctival redness ≥ 2; and/or
  - (iv) Conjunctival oedema (chemosis) ≥ 2
- Calculated as the mean scores following the grading at 24, 48 and 72 hours after instillation of the test material, and which fully reverse within an observation period of 21 days.

12. Deviations from the Study Plan

There were the following deviations from the study plan:

Concerning:

Guidelines / References

Addition of the following guideline:

ISO 10993-12: 2007 "Sample preparation and reference materials"

Reason:

Due to the properties of the test item an extraction was performed according to the above-mentioned guideline.

Concerning:

Test System, p. 10 of the study plan

Before:

Age at the beginning of the study: approximately 13 weeks old

New:

Age at the beginning of the study: approximately 23 weeks old

Reason:

Technical reason.

These deviations did not influence the quality or integrity of the present study.

13. Results

The test item extract produced slight irritant, but no corrosive ocular effects after instillation into the eyes of 3 female rabbits (strain NZW) (tables 3 to 5).

Neither mortalities nor significant clinical signs of toxicity were observed (table 6).

The eyes were not rinsed.

Upon fluorescein examinations at the end of the observation period of 72 h no corneal lesions were found in any animal.

Table 3: Eye Irritation Scores – Animal No. 1

Animal no. 1		Single data				Average score (24, 48 and 72 hours)
		Time post application				
		1 hour	24 hours	48 hours	72 hours	
		T/C	T/C	T/C	T/C	
	Cornea	0/0	0/0	0/0	0/0	0
	Iris	0/0	0/0	0/0	0/0	0
	Conjunctival redness	0/0	0/0	0/0	0/0	0
	Conjunctival chemosis	0/0	0/0	0/0	0/0	0

Table 4: Eye Irritation Scores – Animal No. 2

Animal no. 2		Single data				Average score (24, 48 and 72 hours)
		Time post application				
		1 hour	24 hours	48 hours	72 hours	
		T/C	T/C	T/C	T/C	
	Cornea	0/0	0/0	0/0	0/0	0
	Iris	0/0	0/0	0/0	0/0	0
	Conjunctival redness	0/0	0/0	0/0	0/0	0
	Conjunctival chemosis	0/0	0/0	0/0	0/0	0

T = test item, C = control

Table 5: Eye Irritation Scores – Animal No. 3

		Single data				Average score (24, 48 and 72 hours)
		Time post application				
		1 hour	24 hours	48 hours	72 hours	
		T/C	T/C	T/C	T/C	
Animal no. 3	Cornea	0/0	0/0	0/0	0/0	0
	Iris	0/0	0/0	0/0	0/0	0
	Conjunctival redness	0/0	1/0	0/0	0/0	0.33
	Conjunctival chemosis	0/0	0/0	0/0	0/0	0

T = test item, C = control

Table 6: Individual Data

Individual systemic and local findings									
Time after test item application	*Animal number 1*			*Animal number 2*			*Animal number 3*		
	systemic findings	*specific local findings*	*Comments*	*systemic findings*	*specific local findings*	*Comments*	*systemic findings*	*specific local findings*	*Comments*
1 hour	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
24 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
48 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
72 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-

nsf = no specific findings

13.1. Body Weight Development

There were no significant body weight changes during observation period (table 7).

Table 7: Absolute Body Weights in kg

Animal No.	*Start of Study (Weight kg)*	*End of Study (Weight kg)*
1	4.8	4.8
2	4.2	4.3
3	4.4	4.5

13.2. Conclusions

Under the conditions of the present study, single ocular instillation of the extract of the test item Niobium to rabbits at a dose of 0.1 mL produced slight irritant effects in 1 out of 3 animals, which were fully reversible within 48 hours. Neither mortalities nor significant clinical signs of toxicity were observed.

In conformity with the EC criteria for classification and labelling requirements for dangerous substances and preparations according to Annex VI of Commission Directive 2001/59/EC and Annex I of Regulation (EC) 1272/2008, the test item Niobium does not have to be classified and has no obligatory labelling requirement for eye irritation (for details see *Evaluation of Results*).

14. Distribution of the Report

1 original (paper):	Sponsor
1 copy (paper):	BSL Bioservice
1 copy (electronic):	Sponsor

15. References

BSL BIOSERVICE, Standard Operating Procedures (SOP) No. 11-2-3

Commission Regulation (EC) No 440/2008, L 142, Annex Part B of 30 May 2008 laying down test methods pursuant to Regulation (EC) No. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

EC, 2001: Commission Directive 2001/59/EC of 6th August 2001 adapting to technical progress for the 28th time Council, Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the Classification, Packaging and Labeling of Dangerous Substances. Official Journal of the European Communities, L 225, 21.08.2001

Draize, J.H. (1955)
Dermal Toxicity pp. 46-59
Association of Food and Drug Officials of the U.S., Washington D.C.

Draize, J.H. (1965)
Appraisal of the Safety of Chemicals
in: Foods, Drugs and Cosmetics - Dermal Toxicity pp. 49-52.
Assoc. of Food and Drug Officials of the United States, Topeka, Kansas

EPA Health Effects Test Guidelines
OPPTS 870.2400 Acute Eye Irritation
United States Environmental Protection Agency
Prevention, Pesticides and Toxic Substances (7101)
EPA 712-C-98-195 (August 1998)

ISO 10993-12: 2007 "Sample preparation and reference materials"

Merkblatt zur tierschutzgerechten Haltung von Versuchstieren; Merkblatt 55 Kaninchen; TVT Tierärztliche Vereinigung für Tierschutz

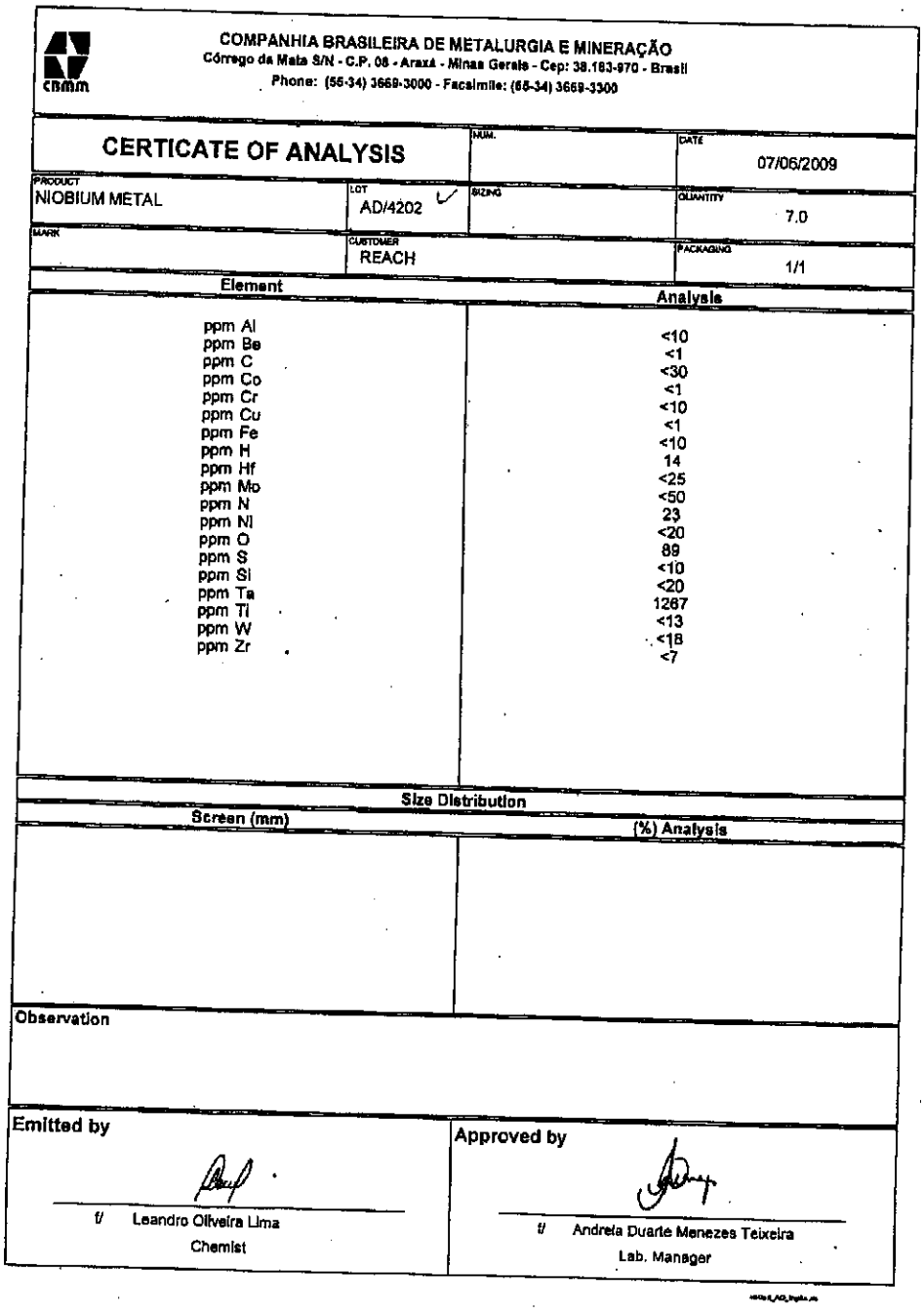
OECD Guidelines for Testing of Chemicals
Section 4: Health Effects
No. 405 Acute Eye Irritation/Corrosion, (2002)
Organisation for Economic Co-Operation and Development, Paris

Planung, Struktur von Versuchstierbereichen tierexperimentell tätiger Institutionen; Veröffentlichung GV-SOLAS (Gesellschaft für Versuchstierkunde, Society for Laboratory Animal Science), Mai 1988

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Communities, L 353, 31.12.2008

Weil, S.C., Scala, R.A., (1971)
Study of Intra- and Interlaboratory Variability in the Results of Rabbit Eye and Skin Irritation Tests.
Toxicol. Appl. Pharmacol. 12: 276-360

16. Appendix - Certificate of Analysis



COMPANHIA BRASILEIRA DE METALURGIA E MINERAÇÃO
Córrego da Mata S/N - C.P. 08 - Araxá - Minas Gerais - Cep: 38.183-970 - Brasil
Phone: (55-34) 3669-3000 - Facsimile: (55-34) 3669-3300

CERTICATE OF ANALYSIS

NUM.	DATE
	07/06/2009

PRODUCT	LOT	SIZING	QUANTITY
NIOBIUM METAL	AD/4202		7.0

MARK	CUSTOMER	PACKAGING
	REACH	1/1

Element	Analysis
ppm Al	<10
ppm Be	<1
ppm C	<30
ppm Co	<1
ppm Cr	<10
ppm Cu	<1
ppm Fe	<10
ppm H	14
ppm Hf	<25
ppm Mo	<50
ppm N	23
ppm Nl	<20
ppm O	89
ppm S	<10
ppm Sl	<20
ppm Ta	1287
ppm Ti	<13
ppm W	<18
ppm Zr	<7

Size Distribution

Screen (mm)	(%) Analysis

Observation

Emitted by

t/ Leandro Oliveira Lima
Chemist

Approved by

t/ Andreia Duarte Menezes Teixeira
Lab. Manager